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Considerations for the combination of anticancer vaccines and immune checkpoint inhibitors

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Abstract

Introduction: Over the past few years, trials evaluating immunotherapies, particularly immune checkpoint inhibitors, have revolutionized the standard model of cancer treatment, demonstrating significant antitumor responses and improved clinical outcomes across a wide array of tumors types. Yet, despite these compelling data, a major limitation has been that only a fraction of patients mount a response to single-agent immune checkpoint inhibition. However, a growing amount of preclinical and clinical data suggests that combining immune checkpoint inhibition, either with other immune checkpoint inhibitors or with therapeutic cancer vaccines, has the potential to improve the proportion of patients seeing long-term durable responses with these therapies.

Areas Covered: We have reviewed the reported data on immune checkpoint inhibition as monotherapy and as combination therapy with other immune checkpoint inhibitors or therapeutic cancer vaccines. Data is reviewed on agents with FDA approval or breakthrough designation as of the writing of this manuscript.

Expert Opinion: Particular focus is given to the combination of immune checkpoint inhibitors and therapeutic cancer vaccines which has the potential to increase efficacy compared to single agent immune checkpoint inhibition with minimal added toxicity.

Keywords

Immune checkpoint inhibitors; therapeutic cancer vaccines; immunogenic intensification

1. Introduction

In recent years, the standard model of cancer therapy has broadened to include novel immunotherapies, based upon growing preclinical and clinical data demonstrating the potential for these agents to produce significant antitumor responses and improved clinical outcomes in a wide variety of tumors. Some of the most promising data have been seen with

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Declaration of interest

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immune checkpoint inhibitors in diseases such as melanoma, lung, renal cell, and bladder cancers. Still, despite these compelling data, a major limitation has been that less than 20% of unselected patients mount a response to single-agent immune checkpoint inhibition.[1] However, emerging preclinical and clinical data suggest that combining immunotherapy agents such as immune checkpoint inhibitors with therapeutic cancer vaccines may increase the percentage of patients who benefit from these therapies.

2. Immune checkpoint inhibitors as single-agent therapy

Ipilimumab, a monoclonal antibody and inhibitor of CTLA-4, was the first immune checkpoint inhibitor to show a survival benefit. It was approved by the US Food and Drug Administration (FDA) after it was found to improve median overall survival (OS) compared to chemotherapy agents (10.0 vs. 6.4 months; hazard ratio [HR] 0.68; $P < 0.001$) in patients with metastatic melanoma.[2] More recently, monoclonal antibodies against programmed cell death 1 (PD-1) and its ligand (PD-L1) have demonstrated impressive clinical efficacy in multiple tumors. In a randomized phase III trial, nivolumab, a PD-1 inhibitor, was compared to dacarbazine or carboplatin, standard second-line chemotherapy options, in patients with metastatic melanoma that had been previously treated with ipilimumab. After 167 patients were followed for at least 6 months, the median overall response rate (ORR) was 32% for nivolumab compared to 11% for chemotherapy. Just as noteworthy, after a median 8.4 months of follow-up, the median duration of response for nivolumab was not reached, with 95% of nivolumab-treated patients still in response, compared to 80% in the chemotherapy-treated group.[3] A phase III trial in patients with previously untreated BRAF-negative melanoma showed that nivolumab produced an ORR of 40% versus 13.9% for dacarbazine (HR 4.06; $P < 0.001$). At 1 year of follow-up, OS was 72.9% in the nivolumab group versus 42.1% in the dacarbazine group (HR 0.42; 99.8% confidence interval [Cl], 0.25–0.73; $P < 0.001$).[4] Based on these data, immune checkpoint inhibitors are now the standard of care for advanced melanoma.

There have also been clinical benefits seen in other tumors beyond melanoma. A phase III trial comparing nivolumab to standard dosing of docetaxel in patients with metastatic squamous non-small cell lung cancer (NSCLC) who had failed at least two prior regimens showed a median OS of 9.2 months for nivolumab versus 6.0 months for docetaxel (HR 0.59; 95% Cl, 0.44–0.79; $P = 0.00025$). The ORR in the nivolumab group was a modest 20%, but, notably, these patients developed durable responses, with a median duration of response still not reached after a median 11 months of follow-up.[5] A similar phase III trial evaluated nivolumab versus docetaxel in patients with non-squamous NSCLC who had failed standard platinum-based doublet chemotherapy. In this study, nivolumab produced a median OS of 12.2 versus 9.4 months with docetaxel (HR 0.73; 96% Cl, 0.59–0.89; $P = 0.00155$).[6] Based on these data, nivolumab was granted FDA approval for previously treated squamous and non-squamous NSCLC.

Nivolumab has also received FDA breakthrough designation for the treatment of subsets of patients with refractory Hodgkin’s lymphoma, based on data in a small cohort of 23 patients showing an ORR of 87%, including 17% with a complete response and 70% with a partial response.[7] Most recently, nivolumab was granted FDA approval for treatment of patients

with advanced renal cell carcinoma (RCC) who had progressed on antiangiogenic therapy, after a phase III trial found that a similar population treated with nivolumab had a median OS of 25.0 months compared to a median 19.6 months with standard second-line everolimus (HR 0.73; 98.5% Cl, 0.57–0.93; $P = 0.002$).[8]

Pembrolizumab, another anti-PD-1 antibody, has also recently gained accelerated FDA approval for use in patients with ipilimumab-refractory advanced melanoma, as well as non-squamous NSCLC. In a large randomized phase I trial in 173 patients with ipilimumab-refractory advanced melanoma, pembrolizumab had an ORR of 26% at both 2 mg/kg and 10 mg/kg.[9] Again, the responses were durable, with a median duration of response not found after a median 11 months of follow-up. In another large phase I trial in 495 patients with metastatic non-squamous NSCLC who had progressed on front-line therapy, pembrolizumab produced an ORR of 19.4%, with a median duration of response of 12.5 months.[10]

MPDL3280A, an anti-PD-L1 antibody, has been granted FDA breakthrough therapy designation for metastatic bladder cancer and NSCLC. In a phase II study of MPDL3280A in 316 patients with metastatic urothelial carcinoma previously treated with platinum-based chemotherapy, the ORR exceeded 15%, with 91% of responses still ongoing after 24 weeks of follow-up.[11] In another phase I trial in 37 patients with NSCLC, MPDL3280A produced a 24% ORR, with all responses ongoing at the time of data analysis.[12] Most recently, Durvalumab, another anti-PD-L1 antibody, has also been granted breakthrough therapy designation for the treatment of urothelial bladder cancer.

In addition, PD-1/PD-L1 inhibition has also been found to produce responses in a fraction of patients with PD-L1 positive triple negative breast cancer as well as mismatch repair deficient colorectal cancers. In a phase lb trial evaluating pembrolizumab (KEYNOTE 012), 5 of 27 (18.5%) patients with PD-L1 positive triple negative breast cancer had an overall response with one patient having a complete response. Median duration of response was not reached after a median of more than 11 months of follow-up. In a phase II study evaluating pembrolizumab in patients with progressive metastatic carcinoma with or without mismatch repair deficiency, 4 of 10 (40%) patients with mismatch repair deficient colorectal cancers had an objective response as compared to 0 of 18 (0%) patients with mismatch repair proficient colorectal cancers.[13] Notably, in this same study, objective responses to anti-PD-1 therapy were also seen in 5 of 7 (71%) patients with mismatch repair deficient non-colorectal cancers suggesting that this deficiency and resulting microsatellite instability may be a marker of response to anti-PD-1 therapy across a number of tumor types.

It has been proposed that mismatch repair deficiency may predispose to response from immune checkpoint inhibition by creating a high somatic mutational and antigenic burden in tumors. Data from the above trial may support this hypothesis as whole exome sequencing of patients enrolled in this trial showed significantly more mutations per tumor in patients with mismatch repair deficient (mean of 1782) versus mismatch repair proficient tumors (mean of 73) (P = 0.007) and found that high somatic mutational burden was significantly associated with longer progression-free survival (PFS) (P = 0.02).[13]

3. Response to anti-PD-1/PD-L1 therapy and correlation with PD-L1 expression

The responses seen with immune checkpoint inhibition in tumors bearing a high mutational burden have been quite promising. Although data are still needed, panels evaluating gene and protein expression of both tumor and immune cells [14] may yet have an important role in predicting patients' responses to treatment in the future.

Still, while results from trials of anti-PD-1/PD-L1 antibodies have suggested deep and durable clinical responses, and predicting these responses may be helpful, a major limitation of these therapies has been that the benefit in terms of ORR has been limited to only about 20% of patients treated.[1] Interestingly, preliminary data suggest that these responses correlate with PD-L1 expression in the tumor microenvironment (TME). Data from studies in melanoma, head and neck, lung, and bladder cancers all suggest that response rates to anti-PD-1/PD-L1 therapy substantially increase in patients who have biopsy-proven PD-L1 expression in the TME.[15–18] In head and neck tumors, response rates have been reported as high as 46% in PD-L1-positive patients, but only 11% in patients whose biopsies had low PD-L1 expression in the TME.[15] Similar findings have been reported in bladder cancer (PD-L1-positive: 43% vs. PD-L1-negative: 11%) [16] and lung cancer (PD-L1-positive: 46% vs. PD-L1-negative: 15%).[17] Even in melanoma, where some of the greatest benefits from anti-PD-1 inhibition have been seen so far, the discrepancy of response among patients with PD-L1-positive tumors and PD-L1-negative tumors has been as high as 49% versus 13%, respectively.[18] In addition, a recent meta-analysis of patients with metastatic melanoma, NSCLC, and RCC showed a significant correlation between response to anti-PD-1/PDL-1 antibodies and PDL-1 expression in the TME.[19] These data suggest that even in cancers where PD-1/PD-L1 inhibition has been most effective, approximately 70–80% of patients are not likely to show significant PD-L1 expression in the TME, which limits any potential benefit from these agents.

4. Rationale for combination immunotherapy

Unlike estrogen receptor status in breast cancer, PD-L1 expression is not static, but rather a dynamic, adaptive response that occurs when tumors encounter immune cells in the TME. Preclinical data indicate that PD-L1 expression within the tumor can be induced by increased exposure to IFN-y, a cytokine produced by activated tumor-infiltrating T cells.[20] Thus, PD-L1 expression is likely a hallmark for a preexisting, underlying immune response. Based on this finding, PD-1/PD-L1 checkpoint inhibition is likely to be most successful in patients who have already developed some degree of antitumor immune response, as evidenced by an increase in PD-L1 expression within the TME. The majority of tumors, however, express very little PD-L1, a sign that they may be lacking the prerequisite tumor-infiltrating immune response necessary to benefit from anti-PD-1/PD-L1 therapies. This probably explains why anti-PD-1/PD-L1 antibodies have induced limited responses in the vast majority of patients.

An ongoing area of research that offers the potential to improve clinical outcomes is immunogenic intensification.[21] This strategy attempts to optimize the antitumor immune

response by combining two different immune checkpoint inhibitors or an immune checkpoint inhibitor and a therapeutic cancer vaccine. Emerging data suggest that a number of immunotherapy agents have the potential to drive activated T lymphocytes into the tumor, resulting in PD-L1 upregulation. This combined immune stimulation using multiple immunotherapies could theoretically increase the number of patients who respond to immune checkpoint inhibition.

5. Preliminary data on immunogenic intensification

5.1. Combining anti-CTLA-4 and anti-PD-1 immunotherapies

CTLA-4 inhibitors activate peripheral T-cell immune responses [22] and have the potential to drive T-cell infiltrates into the TME. Thus, there is a strong rationale for evaluating CTLA-4 inhibitors in combination with PD-1/PD-L1 inhibitors. This combination has induced immune synergy in patients with various tumor types. A phase III trial in previously untreated advanced melanoma (CheckMate 067) randomized 945 patients to receive ipilimumab, nivolumab, or the combination, and found that PFS was 11.5 months (95% Cl, 8.9–16.7) for the combination compared to 2.9 months (95% Cl, 2.8–3.4; $P < 0.001$) for ipilimumab alone and 6.9 months (95% Cl, 4.3–9.5; $P < 0.001$) for nivolumab alone.[23] In patients with PD-L1-positive tumors, median PFS was 14.0 months for the combination group and the nivolumab group; in patients with PD-L1-negative tumors, PFS was longer with the combination therapy than with nivolumab alone (11.2 vs. 5.3 months). The finding that ipilimumab significantly adds to the benefit seen with nivolumab in PD-L1-negative tumors but not PD-L1-positive tumors is consistent with the concept that ipilimumab may potentiate anti-PD-1/PD-L1 therapies by mobilizing a peripheral immune response, leading to lymphocytic tumor infiltration and upregulation of PD-L1 expression in the TME.

Preliminary evidence from the combined use of ipilimumab and nivolumab suggests a potential for improved clinical benefit in both metastatic NSCLC and RCC over single-agent immunotherapy. In CheckMate 016, the combination of these agents was evaluated in 94 patients with advanced RCC: 47 patients who received nivolumab 3 mg/kg and ipilimumab 1 mg/kg, and 47 patients who received nivolumab 1 mg/kg and ipilimumab 3 mg/kg. The reported ORRs for these two regimens was 38.3% and 40.4%, respectively, with a median duration of response of 67.7 and 81.1 weeks, respectively.[24] These ORRs compare quite favorably to the 25% ORR seen with single-agent nivolumab in advanced RCC.[8] In CheckMate 012, nivolumab 1 mg/kg and ipilimumab 1 mg/kg, and nivolumab 3 mg/kg and ipilimumab 1 mg/kg were evaluated in patients with advanced NSCLC. The highest response rate (39%) was seen with nivolumab 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 12 weeks.[25] Again, this response rate compares favorably with the ORR of 19% seen with nivolumab 3 mg/kg alone in patients with advanced NSCLC.[6]

5.2. Combining PD-1/PD-L1 inhibition and therapeutic cancer vaccines

While the addition of ipilumimab to nivolumab has the potential to improve response rates, this benefit comes with the downside of increased toxicity.[23] Therapeutic cancer vaccines, however, have shown limited added toxicity when combined with immune checkpoint inhibitors [26–28] and are believed to also have the potential to prime an antitumor immune

response and broaden the efficacy of PD-1/PD-L1 inhibition. Studies have shown that therapeutic cancer vaccines can activate T cells in the periphery and have the potential to drive these activated T cells into the TME.[29,30]

Even though previous studies in melanoma have not demonstrated that vaccines and immune checkpoint inhibitors can work synergistically,[2] it remains unclear if that is related to the specific vaccines used or the unique TME of melanoma itself. Nonetheless, promising data are emerging from other tumor types. Findings supporting the potential synergistic nature of this combination have come from clinical trials evaluating therapeutic vaccines in prostate cancer, an example of a solid tumor that may benefit from lymphocyte infiltration and PD-L1 upregulation, since baseline PD-L1 expression has been reported to be quite low (< 10%) in this disease.[31]

Sipuleucel-T was approved by the FDA in 2010 for the treatment of minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), based on results of the IMPACT trial, a phase III double-blind placebo-controlled trial in which 512 patients were randomized to receive sipuleucel-T every 2 weeks for a total of 3 doses, or placebo.[32] Patients receiving sipuleucel-T had a 4.1-month improvement in median OS (25.8 vs. 21.7 months; HR 0.78; 95% Cl, 0.61–0.98; $P = 0.03$). A phase II clinical trial evaluated immune response to neoadjuvant sipuleucel-T in 37 patients with localized prostate cancer who were scheduled for radical prostatectomy.[29] Prostatectomy specimens from patients treated with sipuleu-cel-T showed a >3-fold increase in infiltrating $CD3^+$, $CD4^+$, $FOXP3^-$, and $CD8^+$ T cells at the interface of benign and malignant tissue, compared to pretreatment biopsies. In addition, after treatment with sipuleucel-T, nearly half of the $CD3^+$ T cells at the tumor interface expressed PD-1, suggesting a further role for the combination of sipuleucel-T and anti-PD-1 therapy. A phase II trial is currently evaluating sipuleucel-T with and without CT-011 (anti-PD-1) in patients with che-motherapy-naive mCRPC [NCT01420965]. To overcome possible immunosuppression in the TME, this trial is also evaluating low-dose cyclophosphamide in combination with sipuleucel-T and CT-011, as low-dose cyclophosphamide has been shown to selectively reduce $CD4^+$, $CD25^+$, and $FOXP3^+$ T regulatory cells, leading to improved immune responses when combined with vaccine therapies.[33,34]

Evidence of a local immune response in tumor tissue is not limited to sipuleucel-T. Studies evaluating Prostvac, another therapeutic cancer vaccine, show similar findings. Prostvac is a poxviral-based vaccine platform using recombinant attenuated vaccinia and fowlpox viruses containing the gene for prostate-specific antigen (PSA) and three costimulatory proteins: B7–1, LFA-3, and ICAM-1. A phase II randomized trial evaluated Prostvac versus control in 125 patients with minimally symptomatic mCRPC and found a median OS of 25.1 months for those given Prostvac versus 16.6 months for those in the control arm (HR 0.56; 95% Cl, 0.37–0.85; P - 0.0061).[35] These results have led to an ongoing randomized double-blind phase III trial in 1298 patients [NCT01322490]. A phase I study of intraprostatic Prostvac for locally recurrent prostate cancer found a marked increase in $CD4^+$ ($P = 0.0002$) and $CD8^+$ ($P = 0.0002$) T cells in tumor biopsies following therapy.[30]

Preclinical data suggest that, once within the TME, activated T cells produce IFN-y, thereby inducing PD-L1 expression within the tumor.[20] A number of preclinical studies have suggested that the combination of therapeutic cancer vaccine and anti-PD-1 therapy may result in increased antitumor effect. In a murine model of melanoma involving more than 50 mice/treatment group, the group treated with TEGVAX, a toll-like receptor agonist-formulated tumor-cell vaccine, plus anti-PD-1 therapy had sustained tumor regression in >50% of mice compared to minimal regression in mice treated with vaccine or anti-PD-1 therapy alone.[20] Also noteworthy, this antitumor response was negated by blocking IFN-y. In a murine model of HPV E6/E7-expressing tumors, mice 0n = 7/group) treated with an adenovirus-based vaccine against HPV E6 and E7 in combination with anti-PD-1 therapy lived significantly longer ($P < 0.0006$) compared to mice receiving anti-PD-1 therapy alone.[36] In another preclinical study of pancreatic ductal adenocarcinoma, mice treated with an irradiated whole-cell vaccine expressing GM-CSF in combination with anti-PD-1 therapy had significantly improved OS compared to mice treated with anti-PD-1 therapy alone (OS = 81.5 vs. 50 days, respectively; $P = 0.05$).[37] While these preclinical data are promising, the combination of anti-PD-1/PD-L1 antibodies and therapeutic cancer vaccines is just beginning to be evaluated in the clinic (Table 1).

5.3. Combining anti-CTLA-4 and therapeutic cancer vaccines

Another treatment strategy is to employ therapeutic cancer vaccines with immune checkpoint inhibitors such as anti-CTLA-4. Although the phase III study evaluating gplOO and anti-CTLA-4 did not demonstrate improved outcomes,[2] it is unclear if this was unique to the clinical setting or the fact that gplOO is a less immunogenic peptide-based vaccine strategy. Other early-phase clinical trials evaluating anti-CTLA-4 therapy in combination with more modern therapeutic cancer vaccines have shown improved clinical outcomes and manageable toxicities. A phase I trial of GVAX combined with escalating doses of ipilimumab (0.3, 1, 3, and 5 mg/kg) was conducted in men with chemotherapy-naive mCRPC. PSA declined by >50% in 25% of patients, and the median OS of 29.2 months was longer than predicted.[26] A preclinical study evaluating the optimal sequence of ipilimumab and GVAX therapy found that the combination therapy led to enhanced infiltration of $CD8^+$ T cells into the prostate, and that vaccine therapy followed by ipilimumab maximized these results.[38]

A phase I trial of Prostvac with escalating doses of ipilimumab (1, 3, 5, and 10 mg/kg) given monthly was conducted in 30 men with mCRPC. Of the 24 patients who were chemotherapy-naive, 14 (58%) had PSA declines, 6 of which (25%) were >50%.[27] The median OS of patients receiving Prostvac plus ipilimumab was 31.3 months for all cohorts and 37.2 months for those treated with ipilimumab 10 mg/kg. In addition, approximately 20% of patients treated with 10 mg/kg are still alive after 80 months of follow-up.[39] These patients had a median OS substantially longer than those treated in a phase II trial with Prostvac alone (25.1 months), despite the fact that this phase I population had similar baseline characteristics (predicted median OS of 18.5 months). In addition, the median OS seen with this combined regimen is also considerably longer than the median OS seen with sipuleucel-T in the IMPACT trial (25.8 months).[32] These findings are especially notable given that ipilimumab has yet to show independent clinical benefit in mCRPC. A phase III

randomized clinical trial in 799 patients with mCRPC failed to find a survival benefit with ipilimumab versus placebo following limited radiotherapy (median OS 11.2 vs. 10.0 months; HR 0.85; 95% Cl, 0.72–1.00; $P = 0.053$).[40] Results from these trials suggest that the combination of therapeutic cancer vaccines and anti-CTLA-4 therapy could be more efficacious than either agent alone.

Findings suggesting that the combination of immune checkpoint inhibitors with vaccine therapy may produce clinically meaningful benefit even when no benefit is seen with immune checkpoint inhibitors alone are not unique to prostate cancer. Trials evaluating immune checkpoint inhibitors as monotherapy in pancreatic adenocarcinoma have been unsuccessful. No responses were seen in a multicenter phase I trial of anti-PD-L1 in 17 patients with advanced pancreatic cancer.[41] In addition, a phase II trial of single-agent ipilimumab in 27 patients with locally advanced or metastatic pancreatic cancer also showed no responses.[42] The lack of efficacy seen with single-agent immune checkpoint inhibition in both prostate and pancreatic adenocarcinoma is not surprising, since these diseases generally express low levels of PD-L1 in the TME.[31,43]

Early-phase clinical trials suggest that, as with Prostvac and ipilimumab in prostate cancer, therapeutic cancer vaccines combined with immune checkpoint inhibitors may offer clinical benefit in advanced pancreatic cancer. GVAX pancreatic vaccine consists of two irradiated allogeneic pancreatic tumorcell lines engineered to express GM-CSF. It has been shown in early-phase studies to induce T-cell responses to tumor antigens such as mesothelin.[44] In a phase lb trial that randomized 30 patients with previously treated advanced pancreatic cancer to ipilimumab 10 mg/kg with or without GVAX pancreatic vaccine, the median OS analysis favored the combination over ipilimumab alone (5.7 vs. 3.6 months; HR 0.51; $P = 0.072$; 1-year OS 27% vs. 7%).[28]

6. Conclusion

Over the past few years, trials of immunotherapies, particularly of immune checkpoint inhibitors, have revolutionized the standard model of cancer treatment, demonstrating significant antitumor responses and improved clinical outcomes across a wide array of tumors types. These findings are certainly compelling, but results from these same trials also show a limitation of these therapies, that is, that only a fraction of patients treated with immune checkpoint inhibition have responses to these agents. However, a growing amount of clinical data suggest that combining immune checkpoint inhibition, either with other immune checkpoint inhibitors or with therapeutic cancer vaccines, has the potential to improve the percentage of patients seeing long-term durable responses with these therapies.

7. Expert opinion: balancing efficacy and toxicity with combination immunotherapy

One of the downsides of combination immunotherapy is the potential for increased toxicity. In CheckMate 067, 55% of patients with advanced melanoma who received nivolumab plus ipilimumab experienced grade 3 or 4 treatment-related adverse events. This percentage was significantly higher than the 16.3% and 27.3% of patients who developed grade 3 or 4

adverse events with nivolumab or ipilimumab alone, respectively.^] In addition, treatment-related adverse events of any grade led to discontinuation of treatment in 36.4% of the combination group compared with 7.7% in the nivolumab group and 14.8% in the ipilimumab group. The most frequent grade 3 or 4 immune-related adverse events were diarrhea in 9.3% of those in the combination group compared to 2.2% and 6.1% in the nivolumab and ipilimumab groups, respectively, and elevated transaminitis in 8.3% in the combination group compared to 1.3% and 1.6% in the nivolumab and ipilimumab groups, respectively. Colitis occurred in 7.7% in the combination group and 8.7% in the ipilimumab group, but in only 0.6% in the nivolumab group. These data strongly suggest that not only is the combination more toxic than either therapy alone, but that nivolumab is better tolerated than ipilimumab at the doses given.

These data are also consistent with findings from CheckMate 016, which evaluated two different dosage combinations of ipilimumab and nivolumab in patients with advanced RCC. One cohort received nivolumab 1 mg/kg and ipilimumab 3 mg/kg, a dosage similar to that given to the combination group in CheckMate 067. Not surprisingly, a large proportion (64%) of patients in this cohort developed grade 3 or 4 toxicities. However, in the second cohort, which evaluated nivolumab 3 mg/kg and ipilimumab 1 mg/kg, only 34% of patients developed grade 3 or 4 toxicities, suggesting that higher doses of ipilimumab may contribute more to toxicity in combination immunotherapy than increased doses of nivolumab,[24] a noteworthy finding in light of the fact that the ORRs for these two cohorts were similar at 40.4% (cohort 1) and 38.3% (cohort 2). Therefore, while combination immunotherapy has the potential for increased toxicity, these regimens may be optimized to limit toxicity without hindering clinical outcomes.

Moreover, studies have shown that certain immunotherapies, specifically therapeutic cancer vaccines, may be added to immune checkpoint inhibitors with minimal added toxicity. A number of phase I trials have suggested that, unlike combined immune checkpoint inhibition, the addition of therapeutic cancer vaccines to single-agent immune checkpoint inhibitors does not result in added toxicity. A phase I trial of GVAX combined with escalating doses of ipilimumab, as well as a phase I study of Prostvac in combination with increasing doses of ipilimumab, both in patients with mCRPC, showed similar rates of immune-related adverse events in those receiving the combination compared to the rates seen with ipilimumab alone.[26,27] In addition, in a phase lb trial of GVAX with ipilimumab 10 mg/kg in patients with advanced pancreatic cancer, grade 3 or 4 adverse events were seen in only 20% of patients, a rate comparable to ipilimumab alone.[28] The possibility that therapeutic cancer vaccines added to immune checkpoint inhibition may improve clinical outcomes while adding minimally to toxicity makes these agents and their combination with immune checkpoint inhibition a promising treatment strategy for future clinical trials.

Finally, future strategies could incorporate additional immune checkpoint inhibitors now in early stage trials such as TIM-3, OX-40L, and additional immunologic strategies such as oncolytic viruses which have demonstrated independent efficacy could also be combined with the previously discussed immunotherapy strategies.

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Article highlights

- In recent years, monoclonal antibodies against PD-1 and its ligand (PD-L1) have demonstrated impressive clinical efficacy in multiple tumors.
- Data suggest that mismatch repair deficiency may predispose to response from immune checkpoint inhibition by creating a high somatic mutational and antigenic burden in tumors.
- Data suggest that responses to PD-1/PD-L1 blockade may correlate with PD-L1 expression in the TME.
- Emerging data suggest that a number of immunotherapy agents have the potential to drive activated T lymphocytes into the tumor, resulting in PD-L1 upregulation. This combined immune stimulation using multiple immunotherapies could theoretically increase the number of patients who respond to immune checkpoint inhibition.
- The combination of immune checkpoint inhibitors and therapeutic cancer vaccines is of particular interest as it has the potential to increase efficacy compared to single agent immune checkpoint inhibition with minimal added toxicity.

Table 1.

Selected early phase trials of therapeutic cancer vaccines and anti-PD-1/PD-L1 therapy.

GVAX pancreas vaccine (with CY) and CRS-207 with or without nivolumab	(NCT02243371)
A GM-CSF secreting allogeneic pancreatic cancer vaccine with or without nivolumab for the neoadjuvant and adjuvant treatment of surgically resectable pancreatic adenocarcinoma	(NCT02451982)
MPDL3280A with CDX-1401 in NY-ESO 1(+) IIIB, IV, or recurrent NSCLC	(NCT02495636)
Nivolumab with GM.CD40L vaccine in lung adenocarcinoma	(NCT02466568)
PD-1 blockade alone or in conjunction with the DC/RCC fusion cell vaccination	(NCT01441765)
Nivolumab in combination with DC vaccines for the treatment of recurrent grades III and IV brain tumors	(NCT02529072)
pTVG-HP DNA vaccine and pembrolizumab in patients with castration-resistant, metastatic prostate cancer	(NCT02499835)
Sipuleucel-T with or without anti-PD-I mAb (CT-oil) and low-dose cyclophosphamide in men with advanced castrate-resistant prostate cancer	(NCT01420965)
Immune checkpoint inhibition with or without dorgenmeltucel-L (hyper acute melanoma) immunotherapy for stage IV melanoma patients	(NCT02054520)
A vaccine combining multiple class 1 peptides and montanide ISA 51 VG with escalating doses of anti-PD-I antibodyBMS-936558 for patients with unresectable stages III/IV melanoma	(NCT01176461)
Helper peptide vaccine plus PD-1 blockade in advanced melanoma	(NCT02515227)
Blockade of a PD-I in conjunction with the DC/AML vaccine following chemotherapy-induced remission	(NCT01096602)
Blockade of PD-I in conjunction with the DC/myeloma vaccines following stem cell transplantation	(NCT01067287)

DC: Dendritic cell; RCC: renal cell carcinoma.